about which outcome is affected (the Canadian study did not find an association between maternal work with leather and prematurity,[12] but mothers employed as leather workers in Leicestershire, UK, were twice as likely as other manual workers to have a perinatal death[11]). In contrast to maternal occupational exposures, there is little to suggest that paternal exposures are associated with a substantial risk of prematurity. The only exception is perhaps for the children of male ceramic workers, but our finding should be treated with caution, since we have found no other corroborating reports.

The three adverse outcomes studied here are not independent measures of prematurity. Low birthweight and preterm delivery are highly correlated, and RR estimates for each are often similar in the same occupational group. Small-for-gestational age is a composite measure of birthweight and gestational age. It is noteworthy that the risk of this adverse outcome hardly varied between occupational groups; this suggests that occupational factors act by increasing the risk of preterm delivery, rather than by slowing intrauterine growth.

In conclusion, these data indicate that neither maternal nor paternal occupational exposures have strong effects on the risk of prematurity. Where there is evidence of adverse effects, they are associated with maternal rather than with paternal exposures.

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HYPOTHESIS

Adverse reactions to co-trimoxazole in HIV infection

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The origin of the increased frequency of side-effects to co-trimoxazole in HIV-positive patients is unknown. Data on plasma concentrations of the parent compounds are inconclusive. Evidence points to the hydroxylamine derivatives of sulphamethoxazole as the reactive metabolites that cause adverse reactions to co-trimoxazole. HIV-positive individuals have a systemic glutathione deficiency, and therefore a reduced capacity to scavenge such metabolites. This process would lead to an increased exposure to toxic intermediates and would explain the high frequency of adverse reactions to co-trimoxazole in these patients.

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Pneumocystis carinii pneumonia is an important opportunistic infection in patients with the acquired immunodeficiency syndrome (AIDS). Treatment with a high dose of co-trimoxazole—20 mg/kg trimethoprim (TMP) and 100 mg/kg sulphamethoxazole (SMX)—is recommended. The frequency of adverse reactions to co-trimoxazole in patients with AIDS (40–80%) is much higher compared with other patients, even those who are immunodeficient.[1–8] The explanation for this increased side-effect profile is unknown.

Trimethoprim and possible side-effects

Controversy exists as to whether side-effects depend on serum concentrations of TMP.[4–7] Serum concentrations above 25 mg/l in patients with AIDS may be associated with leucopenia, and dose reduction to maintain serum concentrations between 5 and 8 mg/l may reduce the risk of bone marrow suppression while preserving antimicrobial efficacy.[7] Other studies have shown that the serum concentration of TMP was 48% higher in patients treated with TMP and dapsone compared with patients treated with TMP and SMX, whereas adverse events were more common in the TMP/SMX group.[4,8]

TMP inhibits dihydrofolate reductase and can cause megaloblastic anaemia and neutropenia in patients whose folate stores are deficient. In some patients, megaloblastic changes in bone marrow have been found despite normal serum folate concentrations.[6] However, other studies have

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either failed to find megaloblastic changes or report no therapeutic benefit with folinic acid.[1,2] A different mechanism that explains the haematological changes has been described. Antibodies to polymorphonuclear cells have been found in untreated HIV-infected patients and were shown to increase according to the degree of neutropenia in co-trimoxazole-treated AIDS patients.[9] Therefore no convincing data show that TMP is the main cause of the side-effects in such patients, although a contributory role cannot be excluded.

Sulphamethoxazole and possible side-effects

The relevance of serum concentrations of SMX to the development of adverse reactions in AIDS patients is also controversial.[3-5] Some workers do not believe that high serum SMX concentrations are a contributory factor,[3] whereas other groups do share this belief.[5] Other mechanisms may be more important, such as formation of sulphonamide metabolites.

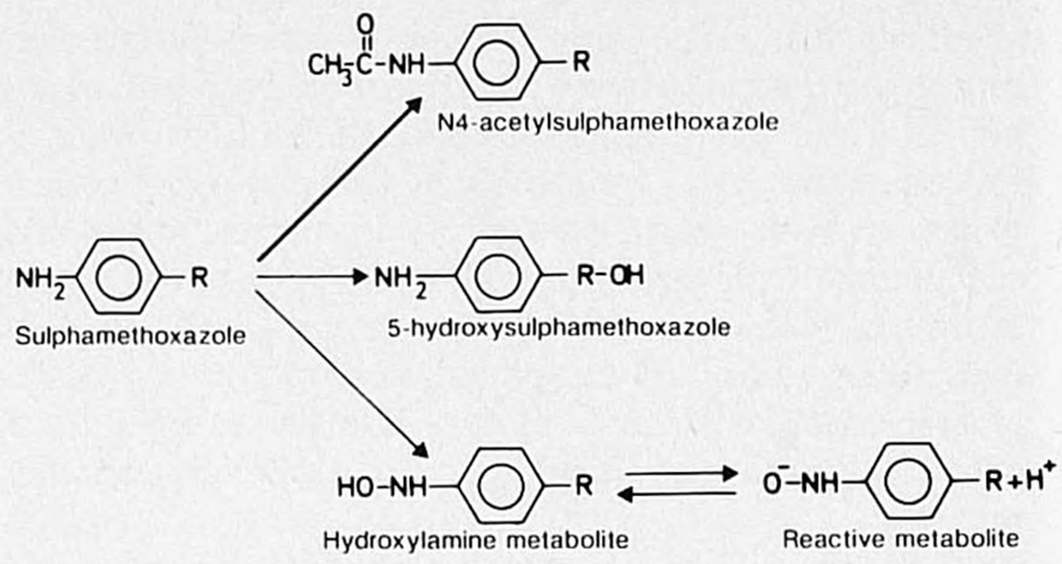
Sulphamethoxazole is metabolised (figure) by N-acetyltransferase (50–70%) to N4-acetylsulphamethoxazole (N4-SMX), and by the cytochrome-P450 system (10–15%) to 5-hydroxysulphamethoxazole (SMX-5OH). SMX can also be oxidised on the N4 position to form a hydroxylamine derivative.[10-13] The rate of production of this reactive intermediate may be influenced by the rate of acetylation of the parent compound,[12] which suggests that acetylator status is important. Inherited differences in the rate of production of this reactive metabolite may also contribute to this process.[13] The hydroxylamine metabolite is an electrophilic, reactive compound that can bind covalently to macroglobulins; it must be scavenged by the oxidant-buffering capacity of glutathione before it is excreted in the urine. In-vitro studies show that hydroxylamine metabolites lead to increased cytotoxicity towards lymphocytes of patients with a clinical history of sulphonamide hypersensitivity compared with control lymphocytes of non-allergic individuals.[10-13] The cytotoxicity of these hydroxylamine derivatives diminished after coincubation with glutathione or N-acetylcysteine.[10,12] Hydroxylamine derivatives may have a direct cytotoxic action because of the ability of these electrophilic species to bind to macroglobulins. This process may lead to formation of haptens that could stimulate an immune response. Scavenging of these hydroxylamine derivatives by glutathione might be crucial for prevention of covalent binding and toxicity. Hypersensitivity may be due to increased production of a reactive metabolite together with the relative inability of tissues to detoxify such a substance.[14]

Glutathione concentrations in HIV-positive individuals

Glutathione is an important antioxidant. In patients with AIDS, as well as in symptom-free HIV-positive individuals, glutathione concentrations in both serum and bronchoalveolar lavage fluid were significantly reduced.[15,16] The mechanisms that lead to this systemic glutathione deficiency are unknown. Decreased glutathione synthesis, increased catabolism, and increased use could all be involved.[16] The reactive metabolites of sulphonamides are scavenged by glutathione.[12] The formation and scavenging of hydroxylamine derivatives takes place throughout the body, since both the cytochrome-P450 system and glutathione are widely distributed.

Hypothesis

The hydroxylamine derivatives of sulphamethoxazole are the reactive metabolites that cause adverse reactions to co-trimoxazole. HIV-positive individuals have a systemic glutathione deficiency, and therefore a reduced capacity to scavenge such reactive metabolites. This process would lead to an increased exposure to toxic intermediates and would explain the high frequency of adverse reactions to co-trimoxazole in these patients. When adverse reactions to co-trimoxazole do occur, dose reduction will often diminish the severity of these events. This observation suggests a dose-related toxicity rather than true hypersensitivity but, as discussed above, measurements of serum concentrations of the parent compounds TMP and SMX do not clearly support this relation. Toxicity may be caused by the metabolite rather than the parent compound. Inherited differences in the rate of production of these (toxic) metabolites, like acetylator status,[13] could add to an individual's susceptibility to adverse events and would explain the lower frequency of side-effects reported in African, Haitian, and black American patients with AIDS.[17,18] The observation that side-effects occur after 8 to 12 days might suggest a role for a metabolite, either by slow accumulation or by an immune response that the metabolite could initiate.



Sulphamethoxazole metabolism.

Although our hypothesis seems attractive because the formation of hydroxylamine derivatives is theoretically likely, detection of these reactive species by methods such as high-performance liquid chromatography, has never been reported. Furthermore, hydroxylamine derivatives can have either a direct toxic effect or function as a hapten, but which of the side-effects of sulphamethoxazole in HIV-positive patients are toxic or immunological remains unclear. In addition, a possible contributory role of TMP cannot be excluded. Like sulphamethoxazole, TMP has a para-amino group that could be oxidised to form hydroxylamines. Glutathione synthesis requires sulphur-containing aminoacids and their metabolism is linked to folic acid and cobalamin; TMP could influence this synthetic pathway.[19]

There are two ways to substantiate this hypothesis. Firstly, N-acetylcysteine could be added to co-trimoxazole treatment. N-acetylcysteine replenishes cysteine and sustains glutathione synthesis when demand for glutathione is increased.[20] Secondly, by selecting sulphonamides that are not easily N-hydroxylated, the generation of reactive metabolites might be prevented. With these modifications of the standard regimens of prophylaxis against *Pneumocystis carinii* pneumonia, side-effects could be largely eliminated.

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BOOKSHELF

Operative Arthroscopy

Edited by John B. McGinty. New York: Raven. 1990. Pp 798. $270/£145. ISBN 0-881676330.

Arthroscopic surgery is now an important orthopaedic subspecialty and for some surgeons represents a large part of their routine workload. Improved instrumentation, such as powered arthroscopy, has led to striking advances in patient management. Gone are the days of admissions to hospital for open arthrotomy; instead a patient is admitted, his or her torn meniscus removed, discharged on the same day, and is soon back to full activity. Thomas Annandale, an Edinburgh professor of clinical surgery who was the first person to open a knee joint to remove a meniscus, undoubtedly would have been impressed.

This very comprehensive book, edited by an acknowledged expert in the discipline, brings together many authorities who have contributed to these advances. It not only includes details about operative arthroscopic techniques but also how to select and use the correct instrument. In the knee, for example, topics such as treatment of synovial plica, always rather a mystery to many surgeons trained in open arthrotomy, are clearly described. There are sections on use of the arthroscope in the shoulder—where is is now possible to repair the rotator cuff, let alone deal with impingement syndrome—and on arthroscopic surgery of the wrist and the elbow. For real afficianados there is even a section on how to examine the ankle joint and achieve tibiotalar arthrodesis. Another section on the temporomandibular joint clearly indicates that no area is safe from the inspecting scope, and probable improvement in patient care. There are excellent and well reproduced illustrations throughout and many background references.

Few prospective clinical trials are yet available on the use of arthroscopic surgery; hopefully they will come, but they cannot really be matched against open surgery in this day and age. But does simple observation, description and resection of an abnormality represent care? In our eagerness to provide symptomatic relief we must not overlook the underlying cause or causes of the abnormalities that we resect: for example, is a medial parapatellar plica in the knee caused by injury, and is this abnormality therefore liable to compensation?

Shorter admissions to hospital and more rapid recovery after surgery are likely to appeal to patients and hospital accountants alike; in the UK, with current concerns about the size of waiting lists for routine orthopaedic operations, many surgeons will also be tempted to put these techniques into practice. In general hospitals it will be important to achieve the right balance between general orthopaedic surgery and arthroscopy, and it may not be necessary for all surgeons to gain and to maintain the necessary experience to practise this specialised technique. Clearly the more recondite and remarkable procedures described in this book will need to be in the hands of surgeons who do little else—although, hopefully, they will occasionally take a broader view of orthopaedic surgery than that seen through their arthroscope.

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Cardiovascular Pathology

Edited by R. Virmani, J. B. Atkinson, and J. J. Fenoglio. Philadelphia: Saunders. 1991. Pp 465. $65/£38. ISBN 0–721632327.

Cardiologists and cardiac surgeons know a fair bit of pathology and a great deal of anatomy. As a pathologist working at a centre with a large cardiothoracic unit, it can be hard work keeping up with one's clinical colleagues. Help is at hand. This excellent book, volume 23 in the *Major Problems in Pathology* series, addresses almost all of the current debates in cardiac pathology and will keep the reader one jump ahead.

This is a problem-based guide rather than a comprehensive textbook of cardiac pathology, with 20